REMARKS

Claims 1, 7, 12 – 17, 19 – 21, 24 – 26, 38 – 48, and 50 – 55 are pending in the application. Of these, Claims 1 and 43 are independent. Each of the foregoing rejections is respectfully traversed. Favorable reconsideration is respectfully requested in view of the above amendments and following remarks.

In the Office Action, all previous prior art rejections were withdrawn. Applicants greatly appreciate the Examiner's indication in this regard, and her associated comments that the claims are now deemed to patentably distinguish from the cited art by reason of "the amendment to the claims and persuasive arguments of Applicant." Applicants also appreciate the Examiner's kind indication in par. 2 that the prior Section 112 rejection of Claims 1, 4-7, 10, 12-17, 19-21, 23-26, 38-39 and 40-42 as allegedly indefinite has been withdrawn in view of the amendments to the claims.

Accordingly, it is Applicants' understanding that the present case is advancing, with certain previous issues having now been resolved, and that it may now be possible to obtain allowance of the claims once the remaining Section 112 enablement issues raised by the Examiner in paragraphs 5 and 6 with respect to Claims 1, 5-7, 10, 12-17, 19-21, 23-26, and 38-55 are satisfactorily addressed.

According to the Examiner, "the specification, while being enabling for specific conditions (E.coli BL21 / DE3 pET3a / P-Fotp5, which is an inducible bacterial system and is grown at 25°C; the washing of inclusion bodies is performed with water or Tris / HCI at a pH8.0), does not reasonably provide enablement for the full breadth of the independent claims." Accordingly, the claims stand rejected as allegedly lacking enablement for substantially the reason stated above.

The Examiner appears to be contending that only claims drawn to the specific embodiments of Applicants' invention are enabled. However, as the Examiner must know, enablement may be found anywhere in the specification, not merely in the examples, and rarely would claims property be deemed enabled only for the specifically disclosed embodiments. This is certainly not such a case.

As explained in MPEP § 2164.02, "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." Hence, the specification need not even contain an example corresponding to what is claimed if the claimed invention is otherwise disclosed in such manner that one skilled in the art could practice a

reasonable range of embodiments within the scope of the claims without undue experimentation. See *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).

It is the Examiner's burden to show an Applicant's claims are not enabled. And this burden may not be met by conclusory allegations that a person of skill could not practice the invention as claimed without having to engage in undue experimentation. As a threshold matter, Applicants contend the Examiner has failed to show by adequate evidence or proofs and/or cogent reasoning why the present disclosure is so lacking that a person of skill who sought to practice the invention, as claimed, would be unable to do so except by engaging in so much experimentation that it would be "undue" within the meaning of Section 112 of the Patent Act. Simply "saying" the disclosure is so deficient that the claims lack enablement does not meet the Examiner's burden. It plainly does not rise to the level of making a prima facie case, and hence, Applicants need not come forward with any evidence/ arguments that the claims are in fact sufficiently enabled.

While believed unnecessary, Applicants will nonetheless undertake to explain why their disclosure is sufficient to enable a person of at least ordinary skill in the art of cellular microbiology to practice the invention without "undue" experimentation. First, Applicants would point out that the claims in this case represent a novel combination of known steps, wherein the arrangement and sequence of steps, the conditions and reagents used, and other aspects set forth in the claims, as a whole, would not have been obvious from the prior art.

Accordingly, the initial step of "expressing G-CSF" as a heterologous protein in an expression system is, in and of itself, not a new step. Nor is the range of cultivation parameters, in and of themselves, new. Rather, it is, among other things, the regulation of these particular cultivation parameters during the expression of the G-CSF and the cultivation of the organism that Applicants have found, in the context of the invention as a whole, to increase the proportion of substantially correctly folded G-CSF protein precursor present in the inclusion bodies in the cell of the organism that contributes to the patentable advance defined by the independent claims.

In like manner, "isolation" of the non-classical inclusion bodies containing this increased proportion of correctly folded G-CSF protein precursors is not, in and of itself, a novel step. That is, isolating inclusion bodies from a cultivation medium, per se, is not believed to be new. Once shown Applicants' claim, as a whole, persons of skill will know full well how to isolate these portions of cellular material, and, in any event, the specification speaks of how to do this.

The same holds true for the optional "washing" step, the "solublization" step, and the purification steps, all of which are, individually, relatively well known to those of skill and can easily be accomplished by persons of skill in the art of cellular micro-biology. Although the conditions and the reagents used in these steps, for example, are believed to be new in the sense that they have never been used before in this arrangement/ sequence of steps, (as, for example, "solublizing" the isolated substantially correctly folded G-GSF precursor under "non-denaturing" conditions, and the ultimate recovery of biologically active G-CSF free from any denaturation or renaturation, all of which are believed to be novel and non-obvious), the basic performance of these steps using these reagents and conditions and sequence, once shown to a person of skill, can easily be undertaken and completed with what the person would know from the "ordinary skill" they possess in the art.

Just like a skilled chef knows how to chop, dice, blend, puree, boil, bake, "salt to taste," and do many things a skilled chef would know how to do and, as a result, could "figure out" how to make a brand new, non-obvious dish or soufflet of some sort form a basic recipe in combination with the skill they possess, a person of ordinary skill in the art of cellular microbiology dealing with genetically modified bacteria will, with the skill set they possess, be able to practice the method of Applicants' claims without having to engage in any "undue" experimentation. The Examiner has failed to show how any step of the claimed method or combination of steps, reagents, conditions, and the like is so "far fetched" or unusual, in and of itself, that a person having at least ordinary skill would be unable to successfully practice embodiments of the invention, as claimed, without undue experimentation.

Just because aspects of this art may present challenges in terms of devising and practicing many embodiments of an invention does not per se foreclose inventors from claiming in a relatively broad manner an invention that advances the art in a relatively broad way. This is such a case. Applicants have determined a new approach for enabling enhanced recovery of correctly folded precursor of heterologous G-CSF protein from cultivated organisms by causing such precursors to accumulate in non-classical inclusion bodies, which exhibit a surprisingly enhanced solubility under non-denaturing conditions to limit adverse effects (i.e. help preserve) the delicate, correctly folded protein precursor.

Again, like a skilled baker presented with a challenging new recipe, the person of skill in the art of microbiology and cellular biology, upon learning of Applicants' new method, would certainly be able to practice the various steps under the defined conditions, etc., using what they

know. Just because no art would have suggested the method steps of Applicants' claims in the order and under the conditions specified to obtain the new, non-obvious results of the claims does not, by any means, indicate that the person of skill would have any unusual difficulty applying the method in practice, knowing what they know, once they are able to comprehend the claimed method. Otherwise, every novel non-obvious method of using the machinery of cellular biology to make new forms of protein and/or proteins in new/better ways would be presumed to lack enablement by virtue of the fact that it is a patentable advance over what is already known.

Applicants' claimed methods have not been shown to be so strange or unusual as to present such overwhelming challenges to the person of skill as to warrant the Examiner's condemnation of the claims as "lacking enablement" or, put another way, as requiring so much experimentation, in actual practice, that the level of experimentation would be deemed "undue" compared to what persons of skill in the art are used to having to do.

Insofar as the mode of practicing the method is concerned, the present specification describes a significantly broader range of conditions than the Examiner appears to recognize. For instance, the application teaches at page 13 that the cultivation temperature is preferably from about 20 to 30 °C, not only 25 °C, as contended by the Examiner. Applicants provide examples which compare the results of cultivation within this range of temperatures with cultivation outside of this range (at 37°C and 42°C). These demonstrate that the disclosure would not be viewed by a person of ordinary skill as limited to merely the 25 °C condition used in certain examples of the specification. Likewise, at page 15, Applicants teach that washing may be done with acetate buffer or citrate buffer, not just the water and Tris / HCl buffer mentioned by the Examiner. Page 15 also teaches that non-denaturing pH may be practiced at pH's "below 10," rather than the single pH of 8.0 mentioned by the Examiner.

As mentioned above, patent claims are enabled in accordance with Section 112 if the accompanying specification contains sufficient information regarding the subject matter of the claims to enable one skilled in the pertinent art to make and use the claimed invention without and "undue" experimentation. MPEP §2164. Thus the test of enablement is not whether "some" or even a "lot" of experimentation may be necessary, but whether, if necessary, any amount of experimentation is "undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). The fact that significant experimentation may be required and may be complex does not in and of itself make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983),

aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

Whether the amount of experimentation is "undue" may be analyzed using the factors outlined in the Wands decision. These factors include: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

In the present case, all relevant factors weigh in favor a finding that the present claims are enabled. The present claims, as amended, are not overly broad as they are limited to a single protein type (G-CSF) expressed in a single bacterium species (*E. coli*). Moreover, working examples are given in the specification, from which those of skill in the art can easily extrapolate without undue experimentation. These examples, together with the remainder of the specification, provide significant guidance from the inventors to assist the person of skill in practicing claimed subject matter. Further, the state of the art in this field of technology is relatively well-developed, in general, as discussed above, and the level of ordinary skill in the field of biotechnology arts is relatively high. Both of these factors significantly reduce the amount of experimentation which one of ordinary skill might need to conduct, if any, in order to practice the claimed invention. As described above, persons of skill know how to carry out the individual basic steps in the claimed methods, in and of themselves, (not necessarily the specific novel conditions, reagents, or sequences used, as discussed earlier) and can readily adopt and apply their "ordinary skill" to practice the combination of steps and conditions upon comprehending the overall methods in light of the teachings in the specification. Weighing all of the factors together then, it is apparent that the subject matter of the present claims is more than adequately enabled under the *Wands* analysis.

In view of the foregoing, Applicants have amended independent Claims 1 and 43 more in accordance with the scope of the subject matter enabled in the present disclosure. In view of these amendments, dependent Claims 5, 6, 10, 23, and 49 have been cancelled, without prejudice.

In light of the foregoing, Applicants urge the Examiner to reconsider the application, to withdraw the rejections, and to issue a Notice of Allowance at the earliest possible convenience.

In the event this response is not timely filed, Applicants hereby petition for the appropriate extension of time and request that the fee for the extension along with any other fees which may be due with respect to this paper be charged to our Deposit Account No. **12-2355.**

Respectfully submitted,

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